





COMMENTARY

Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)

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The coronavirus disease 2019 (COVID-19) pandemic has affected every part of the world, causing major morbidity and mortality as well as impacting heavily on the economy of every nation. As for other infectious diseases, vaccination is seen as the primary way to control the infection. A number of vaccines against COVID-19 have now been approved internationally. The AstraZeneca Oxford (AZ) COVID-19 vaccine was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK regulator, on December 30, 2020, and by the European Medicines Agency (EMA), the European regulator, on January 29, 2021. This is one of the most widely used COVID-19 vaccines worldwide.

Concerns about a high number of unusual thrombotic events following vaccination with the AZ vaccine started to grow in early March 2021. On March 11, 2021, both the MHRA and the EMA provided reassurance that the number of events observed was no higher than expected and advised the continued use of this vaccine as the benefits outweighed the risks.^{1,2} Within a week, however, researchers from Norway, Germany, and the United Kingdom reported on a group of patients who had been previously healthy but were admitted within 3 weeks of AZ vaccination with an unusual combination of cerebral venous sinus thrombosis (CVST) and

thrombocytopenia. All three groups independently identified that their patients had circulating antibodies against platelet factor 4 (PF4), which were detected using the heparin-induced thrombocytopenia (HIT) ELISA assay.

Schultz and colleagues³ from Norway reported on five patients admitted to the hospital with thrombosis (four CVST, one portal vein) and thrombocytopenia 7 to 10 days after AZ vaccination. In Norway, health care personnel younger than 65 years were selected to receive the AZ vaccine first, and the five cases appeared after 132 686 first doses of the vaccine were administered. Three of the women were on hormonal therapy. All five patients had high levels of IgG against PF4-polyanion complexes and also had platelet activation detected with a functional assay.³

Greinacher and colleagues⁴ from Germany and Austria reported on 11 patients who presented 5 to 16 days after AZ vaccination with multiple thromboses and thrombocytopenia. Nine of the patients had CVST, three had splanchnic vein thrombosis, three had pulmonary embolism, and other types of thrombosis were detected in four patients. In one patient who died from cerebral bleeding, CVST could not be excluded. Using an ELISA assay, the authors showed that the patients had circulating antibodies against PF4-heparin and

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also that there was platelet activation which could be inhibited by immune globulin providing support for a proposed treatment for this condition.⁴

In a report of the early UK experience, Scully and colleagues⁵ described 23 patients presenting 6 to 24 days after AZ vaccination with thrombosis and thrombocytopenia. CVST was the most common type of thrombosis, with many patients presenting with thrombosis in several locations. Although the thrombotic events were primarily venous, two patients had ischemic strokes in the middle cerebral artery territory, one had a myocardial infarction, and one had an aortic thrombus. Patients were positive for anti-PF4 antibodies on two HIT ELISA tests, findings that were confirmed using a functional assay. A case of thrombocytopenia without thrombosis was also described in this paper with equivalent laboratory findings to those with thrombosis, distinguishing it from a typical postvaccine immune thrombocytopenia.⁵ Although these three papers described cases after AZ vaccination, a case report of a 48-year-old woman who presented with CVST and thrombocytopenia 14 days after vaccination with the Johnson & Johnson (J&J) vaccine was recently published. The patient went on to develop splanchnic vein thrombosis, and a HIT ELISA test was positive.⁶ The rollout of vaccination with the J&J vaccine has recently been paused due to reports of six further cases that have the same clinical and laboratory phenotype as those occurring after the AZ vaccine. The characteristics of the published cases are shown in Table 1.

The unusual combination of CVST and thrombocytopenia is very rarely encountered in medicine, and the presentation of so many cases over a very short period alerted clinicians to the possibility of a new syndrome. Although the papers published in the *New England Journal of Medicine* named this VITT to refer to vaccine-induced immune thrombotic thrombocytopenia,³⁻⁵ we feel it would be better if the acronym referred to vaccine-induced immune thrombocytopenia and thrombosis to avoid confusion with thrombotic thrombocytopenic purpura.

VITT shares many similarities with a condition in which hematologists are well versed called heparin-induced thrombocytopenia. HIT is a highly prothrombotic condition that develops 4 to 10 days after heparin exposure and presents with a falling platelet count, which is

often associated with venous or arterial thrombosis. The etiology is the formation of antibodies against the complex of PF4 with heparin, which activate platelets through the Fc gamma RIIA receptor. The condition is managed by avoiding any further heparin exposure and using a nonheparin product as either primary or secondary thromboprophylaxis.⁷ Guidelines recommend that prophylactic platelet transfusions are avoided.⁸

It was noted more than 10 years ago that a condition similar to HIT could rarely occur without heparin exposure, and the condition was termed *spontaneous*⁹ or *autoimmune HIT*.¹⁰ It remained extremely rare, or at least it was recognized extremely rarely.¹⁰ These patients developed anti-PF4 antibodies without exposure to heparin.

So far, VITT has been reported only after the AZ and J&J COVID-19 vaccines, which are based on replication-incompetent adenoviral vectors (Chimpanzee ChAdOx1 for AZ and Human Ad26.COV2.S for J&J). It is likely that an anionic molecule present in the vaccine or produced by the cells at the vaccination site binds to PF4 (a cationic molecule), inducing antibody formation. As with HIT, these antibodies bind to platelets via the Fc gamma RIIA receptors leading to platelet activation. At the time of writing, it remains unclear which component of the vaccine is responsible for causing the production of anti-PF4 antibodies; it could be the adenovirus itself, the spike protein cassette, or other constituents of the vaccine such as polysorbate 80. Furthermore, it is not clear whether this constituent acts as a hapten or whether it is due to molecular mimicry (sequence homology between PF4 and a part of the spike protein).

Patients with VITT are typically admitted to the hospital 5 to 24 (median, 10-12) days after AZ or J&J vaccination with atypical (unusual site) thrombosis and thrombocytopenia (Table 2). The majority of thrombotic events reported so far have been CVST or portal vein thrombosis. More typical venous thrombotic events such as deep vein thrombosis or pulmonary embolism have also been reported. Arterial events such as bilateral leg ischemia, myocardial infarction, or stroke constitute at least 10% of acute admissions. Overall age of presentation is <60 years, and although in the reports from Norway

TABLE 1 Summary of the reported cases of vaccine-induced immune thrombocytopenia and thrombosis

Reference	Vaccine	Country/ Area	Number	Age, y, mean (range)	Sex	Primary thrombosis type	Platelet count, ×10 ⁹ /L, mean (range)	Outcome
Schultz et al ³	AZ	Norway	5	40.8 (32–54)	4 F, 1 M	4 CVST 1 portal vein	27 (10–70)	Fatal 60%
Greinacher et al ⁴	AZ	Germany and Austria	11	36 (22–49)	9 F, 2 M	9 CVST 1 PE	35 (8–107)	Fatal 55%
Scully et al ⁵	AZ	United Kingdom	23	46 (21–77)	13 F, 10 M	13 CVST 4 PE 1 DVT 2 MCA strokes 2 portal vein	44 (7–113)	Fatal 30%
Muir et al ⁶	J&J	United States	1	48	1 F	1 CVST	13	Critically ill at reporting

Abbreviations: AZ, AstraZeneca; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; F, female; J&J, Johnson & Johnson; M, male; MCA, middle cerebral artery territory; PE, pulmonary embolism.

TABLE 2 Clinical features and management of vaccine-induced immune thrombocytopenia and thrombosis

Presentation
 Vaccine: AstraZeneca or Johnson & Johnson
 Timing: 5-24 days after vaccination
 Dose: Mostly after the first dose
 Thrombosis: Often atypical and multiple; CVST and portal vein thrombosis most common
 Thrombocytopenia: Variable but often $<20 \times 10^9/L$
 Fibrinogen: Often reduced to 1.0-2.0 g/L
 D-dimer: Raised often to 4000-60 000
 Anti-PF4: Positive by HIT ELISA

Current management
 Give intravenous immunoglobulin
 Avoid platelet transfusions
 Avoid heparin-based anticoagulants
 Use alternative anticoagulants such as argatroban, fondaparinux, or DOAC
 Consider plasma exchange in nonresponding cases
 Early recourse to neurosurgery to relieve raised intracranial pressure

Abbreviations: CVST, cerebral venous sinus thrombosis; DOAC, direct oral anticoagulant; HIT, heparin-induced thrombocytopenia; PF4, platelet factor 4.

and Germany it was mostly women, in the United Kingdom we are seeing a more equal sex distribution. One possible reason for this variation is the different national rollout schedules, which in Norway and Germany concentrated on health care workers, where there is a female excess. A further striking similarity between the current published cases is the significant mortality, ranging from 30% to 60% (Table 1). The platelet count tends to be lower than that seen with HIT, and there is often a reduction in fibrinogen and a marked elevation in the D-dimer levels. Patients have strongly positive anti-PF4-polyanion or anti-PF4-heparin antibodies detected by the HIT ELISA, but the HIT chemiluminescence assays are often negative. This most likely reflects the different specificities of the assays to heparin itself.

The management of patients is extrapolated from the treatment of autoimmune HIT, consisting of avoiding platelet transfusions and heparin exposure and using intravenous immunoglobulin (IVIG).¹¹ Our UK experience is that it is important to give high-dose IVIG early to turn off the prothrombotic process. Given the similarities to HIT, anticoagulation is currently provided through nonheparin anticoagulants such as argatroban, fondaparinux, or the direct oral anticoagulants. Anticoagulation is more challenging in patients with marked thrombocytopenia such as those with platelet counts $<30 \times 10^9/L$ since severe bleeding into the brain is more common than with non-vaccination-related CVST or with HIT. In many of the patients who died with VITT, the cause of death was intracerebral hemorrhage. Intervention in very extensive CVST with thrombectomy and/or neurosurgery should be considered, and an early discussion with neurosurgery is advised.¹² Transfusion to correct hypofibrinogenemia and thrombocytopenia are recommended before invasive procedures. Uncertainties remain, such as the value of steroids, whether heparin can be used safely in all cases and the benefits versus risks of prophylactic platelet transfusion other than for surgery.

It is important to appreciate that it is <6 weeks since the possibility of an unusual thrombotic pattern after the AZ vaccination was considered. We are bound to learn more in the next few weeks or months, including the true incidence, the optimal management, and, importantly, the length of time the antibodies persist as well as whether or not antibody persistence will be associated with recurrence of VITT. In particular, we do not know the natural history of the antibody in terms of persistence and expression of disease. We are concerned that it may persist for months and we may need to give repeated treatment for thrombocytopenia. Thus, any patients who present with this condition need close follow-up, with measurement of anti-PF4 antibodies and routine laboratory parameters, such as platelet count and D-dimer and fibrinogen levels.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

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